

Middle East Respiratory Syndrome Coronavirus and Severe Acute Respiratory Syndrome Coronavirus

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Abstract

Keywords

- MERS
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Emerging infectious diseases continue to be of a significant importance worldwide with the potential to cause major outbreaks and global pandemics. In 2002, the world had witnessed the appearance of the severe acute respiratory syndrome coronavirus in China which disappeared abruptly within 6 months. About a decade later, a new and emerging novel coronavirus named the Middle East respiratory syndrome coronavirus (MERS-CoV) was described in a patient from Saudi Arabia. These two coronaviruses shared multiple similarities in the epidemiology, clinical presentations, and posed challenges in its prevention and management. Seven years since its discovery, MERS-CoV continues to be a lethal zoonotic pathogen capable of causing severe pneumonia with high case fatality rates and the ability to cause large health care-associated outbreaks.

Emerging infectious diseases continue to be of a significant importance worldwide with the potential to cause major outbreaks and global pandemics. In 2002, the world had witnessed the appearance of the severe acute respiratory syndrome coronavirus (SARS-CoV) in China.^{1,2} And about a decade later, a new and emerging coronavirus was described in a patient from Saudi Arabia.^{3,4} The virus was identified as a novel coronavirus and later was named the Middle East respiratory syndrome coronavirus (MERS-CoV).⁵ These two coronaviruses shared multiple similarities in the epidemiology, clinical presentations, and posed challenges in prevention and management.^{6,7} For any new emerging zoonotic pathogen, there are five stages in the evolution to cause diseases limited to humans. In stage 1, the pathogen is confined to the animal host; in stage 2, human infections occur as a result of animal contacts; in stage 3, there is a limited human-to-human transmission; stage 4, there are

multiple outbreaks with human-to-human transmission; and stage 5, infections occur within humans.⁸ In this review, we describe the epidemiology, clinical features, and outcome of both SARS and MERS-CoV.

The SARS-CoV and MERS-CoV

SARS-CoV and MERS-CoV are enveloped positive strand RNA betacoronaviruses. The first coronavirus was isolated from humans in 1965 and was cultivated on human ciliated embryonal tracheal cells.⁹ Coronaviruses are enveloped, and positive stranded RNA viruses classified as a family within the Nidovirales order. There are four genera: α , β , gamma, and delta, and human coronaviruses belong to the α or the β genera.¹⁰ In 2002, SARS-CoV outbreak was described and the virus was 50 to 60% identical and distantly related to known coronaviruses.¹¹ The newly described virus was able

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to cause disease in macaques with a similar spectrum of disease.¹² While the MERS-CoV belongs to lineage C beta-coronavirus and emerged in September 2012 and continuous to cause sporadic cases and clusters of disease mostly in the Arabian Peninsula.¹³

SARS Outbreak Evolution and Clinical Characteristics

The initial description of the SARS outbreak was announced in November 2002 through non-official reports of the occurrence of an outbreak of respiratory illness in Guangdong Province, China,¹⁴ and few months later, this was reported to the World Health Organization (WHO). Analysis of the virus showed a point-source outbreak.¹⁵ The disease was recognized due to the occurrence of a cluster of atypical pneumonias occurring in Vietnam, Hong Kong, Canada, United States, and Singapore.^{1,16–23} All cases were linked to a patient who stayed in hotel M in Hong Kong, and subsequently, patients traveled from Hong Kong to Ireland, Vietnam, Singapore, United States, and Canada.²⁴ This outbreak involved 30 countries in 6 continents and caused a total of 8,098 cases with a case fatality rate of 9.5%.²⁵ The clinical spectrum of the disease ranged from mild to severe disease requiring mechanical ventilation.²⁶ The clinical picture followed an initial febrile illness, followed by a period of improvement then a clinical deterioration.^{27–29} The need for intensive care unit (ICU) care was described in 17 to 30% of SARS patients.^{28–30} In another study, 15% of SARS patients required mechanical ventilation.²⁷ Patients also had extra-respiratory symptoms such as diarrhea.³¹ It was interesting to note that health care workers (HCWs) constituted 21% of all SARS cases.^{32–34} The disease was associated with 10% case fatality rate,³⁵ and the presence of diabetes mellitus and other comorbidities was associated with increased fatality rates.³⁰ SARS was thought to cause milder disease in children with no fatalities.³⁶ One reason for the rapid spread of SARS was the occurrence of superspreaders.³⁵ Superspreading event is described as the ability of certain individuals to infect a disproportionately large number of secondary patients relative to a typical infectious individual.

The origin of the SARS virus is thought to be animal and a similar virus was isolated from Himalayan palm civets (*Paguma larvata*), raccoon dogs (*Nyctereutes procyonoides*), and from a Chinese ferret badger (*Melogale moschata*).³⁷ In addition, antibodies against SARS-CoV were found among wild animal traders in Guangdong Province.^{37,38} A seroprevalence of 72.7% was well known among those with trading history involving *P. larvata*.³⁸ Although most patients with SARS had symptomatic disease, there are few seroprevalence studies and one study showed that 124 (12%) of 1,030 individuals were positive by ELISA and 0.19% by the SARS-specific immunofluorescence assay (IFA).³⁹ In another study, seroprevalence among HCWs was 2.3%⁴⁰ and a meta-analysis showed an overall seroprevalence of 0.10%.⁴¹ There were no approved therapeutic or preventative options for SARS, while a variety of therapeutic agents were used.⁴² SARS human cases disappeared abruptly by June 2003 with no approved vaccine or therapeutic agents developed or applied.

MERS-CoV Evolution and Origin of the Virus

The first case of MERS-CoV was reported in a businessman who lived in Bisha, Kingdom of Saudi Arabia (KSA) who presented to health care with pneumonia in early June 2012 and on transfer to a hospital in Jeddah, he rapidly succumbed to death within 10 days of diagnosis with multiorgan failure. The virus was later isolated and reported in September 2012 as the newly emerging MERS-CoV. As of January 2020, there have been a total of 2,468 cases of human MERS-CoV cases reported to WHO from 27 countries. More than 80% of cases have been reported from the Arabian Peninsula with KSA being the most affected country. There have been 851 reported mortalities with an overall case fatality rate of MERS-CoV estimated at 35% (► Fig. 1). The exact origin of MERS-CoV is not known. However, MERS-CoV is likely to have originated from bats based on the isolation of other lineage C β -coronaviruses closely related to MERS-CoV and the isolation of a bat coronavirus that resembles MERS-CoV. Throat swabs, urine, feces, and serum samples were collected from wild bats in the KSA including the area where the first MERS-CoV patient had lived and worked. A 190-nucleotide fragment of the RNA-dependent RNA polymerase region of MERS-CoV genome was detected in one fecal pellet from an Egyptian tomb bat (*Taphozous perforates*).⁴³ The amplified sequence was identical to that of the MERS-CoV sequence from the first index human case.⁴³ The one-humped dromedaries (*Camelus dromedarius*) had been linked to MERS-CoV (► Fig. 2). Multiple studies showed high prevalence of MERS-CoV antibodies in dromedary camels in the Arabian Peninsula, North Africa, and Eastern Africa.^{44–50} In addition, studies have shown that MERS-CoV antibodies were present in stored camel sera as early as early 1990s, suggesting the presence of MERS-CoV in dromedaries for over 20 years before its first description in humans.^{50–52} MERS-CoV antibodies were detected more commonly among camels > 2 years of age compared with younger camels.^{46,52–54} In addition, MERS-CoV was detected from respiratory tract samples by reverse transcriptase polymerase chain reaction (RT-PCR) in oronasal and fecal samples from dromedary camels in the Arabian Peninsula.^{52–58} In contrast to the MERS-CoV antibodies, juvenile camels shed more MERS-CoV as detected by PCR.^{52–55} In addition, viable MERS-CoV was isolated in cell cultures from nasal and fecal samples from dromedary camels.^{54,57,59–61} There had been studies documenting the isolation of similar and near-identical MERS-CoV strains from epidemiologically linked humans and dromedary camels.^{61–63} In addition, sequence of the MERS-CoV spike, ORF3–4a, and nucleocapsid regions were identical from asymptomatic contacts and their camels.⁶⁴ The most recent common ancestor of all human MERS-CoV was found phylogenetically to date to the end of the year 2010.⁶⁵ In addition, animal reservoir is geographically dispersed.^{66,67}

Clinical Features and Laboratory Findings

The clinical and laboratory presentations of SARS-CoV and MERS-CoV are similar with some minor differences highlighted in ► Table 1. The clinical picture of MERS-CoV cases ranges from asymptomatic to severe cases. In many cases, the presenting

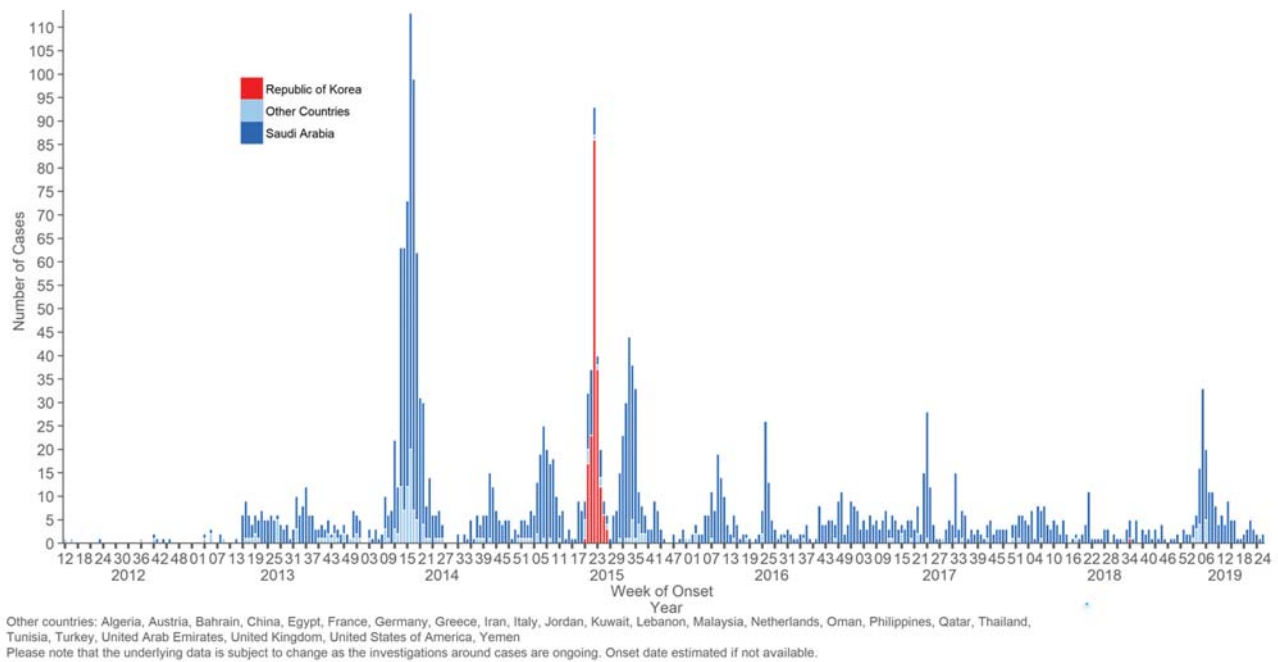


Fig. 1 Epicurve of confirmed global cases of MERS-CoV from September 2012 to July 16, 2019. MERS-CoV, Middle East respiratory syndrome coronavirus; WHO, World Health Organization.

symptoms are respiratory and 33% of patients have gastrointestinal symptoms such as vomiting and diarrhea.^{68–73} Most hospitalized MERS-CoV patients present with fever, cough, and shortness of breath with clinical and radiological evidence of pneumonia.^{70–72,74} It seems that severe disease is a characteristic of primary cases, immunocompromised, and those with underlying comorbidities namely diabetes, kidney, and heart disease. In severe cases, there are multiple complications including respiratory and renal failure, acute liver injury, cardiac arrhythmias, and coagulopathy.^{69,70,73,75} There are few studies which showed no predictive signs or symptoms to differentiate patients with community-acquired pneumonia from those with MERS-CoV infection.^{72,76} The median incubation period was 5.2 days (95% confidence interval [CI], 1.9–14.7), and the serial interval was 7.6 days (95% CI,

2.5–23.1).⁶⁹ The median time to hospitalization, ICU admission, mechanical ventilation, and death were 5, 7, and 11 days, respectively.^{69,77} MERS-CoV carries a high case fatality rate (28.6–63.6%) specially among elderly patients with several comorbidities, while in young healthy patients, they present with mild to no symptoms.^{71,78} One study found a lower case fatality rate similar to the rate reported in patients from South Korea of 9%.^{79,80} The variability of the case fatality rates may be related to host factors, associated comorbidities, care provided, and yet unidentified factors.⁷⁸ In addition, the case fatality rate is inversely related to the percentage of asymptomatic cases as the percentage of these patients increased to 29%, and the case fatality rate decreased to 30%.^{70,71,77,81–83} In addition, the case fatality rate is higher among critically ill patients^{76,78–80} comparing between MERS-CoV and non-MERS-CoV patients in relation to age, clinical, and laboratory features.^{72,76,84–86} In KSA, extensive testing for MERS-CoV is being done over the past 6 years with > 50,000 patients presenting to emergency care with respiratory symptoms being screened for MERS-CoV each year with a very low yield of 0.7% being positive.⁸⁷ This excessive testing is applied in combination with a visual triage in all emergency rooms of all health care facilities (governmental and private) utilizing a clinical score cutoff of > 4 for MERS-CoV infection showing sensitivity and specificity of 74.1 and 18.6%, respectively, in predicting MERS-CoV diagnosis.⁸⁸

Predictors of 30-day mortality included factors such as age > 65 years, being a non-HCW, the presence of preexisting comorbidities, presentation with severe disease, hospital-acquired infections, and corticosteroid use.^{70,89–91} The use of continuous renal replacement therapy and extracorporeal membrane oxygenation (ECMO) were additional risk factors for increased fatality.^{91–93} However, one study showed ECMO lowering in-hospital death.⁹⁴



Fig. 2 Camels: a possible intermediary source of Middle Eastern respiratory syndrome coronavirus.

Table 1 Comparison of demographic, clinical, and laboratory features between MERS-CoV and SARS-CoV

	MERS-CoV ^{8,36–39}	SARS-CoV ^{1,28,40}
Date of first case report (place)	April 2012 (Jordan) June 2012 (first KSA case)	November 2002 (China)
Incubation period	Mean: 5.2 d (95% CI: 1.9–14.7)	Mean: 4.6 d (95% CI: 3.8–5.8)
Range: 2–13 d	Range: 2–14 d	
Serial interval	7.6 d	8.4 d
Age group		
Adults	98%	93%
Children	2%	5–7%
Age (y): range, median	Range: 1–94; median: 50	Range: 1–91; mean: 39.9
Mortality		
CFR—overall	41.8%	9.6%
CFR in patients with comorbidities	13.3%	1–2%
Time from onset to death	Median 11.5 d	Mean 23.7d
Sex (M, F)	M: 64.5%, F: 35.5%	M: 43%, F: 57%
Presenting symptoms		
Fever >38°C	98%	99–100%
Chills/rigors	87%	15–73%
Cough	83%	62–100%
Dry	56%	29–75%
Productive	44%	4–29%
Hemoptysis	17%	0–1%
Headache	11%	20–56%
Myalgia	32%	45–61%
Malaise	38%	31–45%
Shortness of breath	72%	40–42%
Nausea	21%	20–35%
Vomiting	21%	20–35%
Diarrhea	26%	20–25%
Sore throat	14%	13–25%
Rhinorrhea	6%	2–24%
Comorbidities	76%	10–30%
Diabetes	10%	24%
Chronic renal disease	13%	2–6%
Chronic heart disease	7.5%	10%
Malignancy	2%	3%
Hypertension	34%	19%
Obesity	17%	N/A
Smoking	23%	17%
Viral hepatitis	Not known	27%
Laboratory results		
CXR abnormalities	100%	94–100%
Lymphopenia ($<1.5 \times 10^9/L$)	32%	68–85%
Leukopenia ($<4.0 \times 10^9/L$)	14%	25–35%

(Continued)

Table 1 (Continued)

	MERS-CoV ^{8,36–39}	SARS-CoV ^{1,28,40}
Thrombocytopenia ($<140 \times 10^9/L$)	36%	40–45%
Elevated LDH	48%	50–71%
Elevated ALT	11%	20–30%
Elevated AST	14%	20–30%
Ventilatory support required	80%	14–20%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFR, case fatality rate; CI, confidence interval; CXR, chest X-ray; KSA, Kingdom of Saudi Arabia; LDH, lactate dehydrogenase; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

Source: Reproduced with permission from Hui et al.¹⁶¹

Laboratory Tests

The diagnosis of MERS-CoV infection relies on the confirmation by real-time reverse transcriptase PCR of respiratory tract samples. Lower respiratory samples provide better yield and is the sample source of choice for testing.^{95,96} However, a single negative test should not rule out infection and a repeat testing is indicated as some patients may have intermittent positive tests.⁹⁷ Serologic testing for MERS-CoV utilizes IFA, serum neutralization, or protein microarray assays to detect MERS-CoV antibodies.⁹⁸ The utility of serodiagnosis relies on two serum samples taken 14 days or more apart. Serodiagnosis begins with a screening ELISA or IFA and a confirmatory neutralization assay.^{99–101} Testing for MERS-CoV by PCR detected the virus in the patient serum, urine, and feces but at a much lower level than those found in the lower respiratory tract.¹⁰² Patients with MERS-CoV infection had abnormal laboratory findings including: leukopenia, lymphopenia, thrombocytopenia, and elevated hepatic enzymes.^{68,71,72,76,103} A risk analysis showed that the following were associated with increased risk of death: presence of comorbidity (relative risk [RR] = 3), male gender (RR = 1.6), exposure to dromedary camels (RR = 1.6), and consumption of camel milk (RR = 1.5).¹⁰⁴ Overall, over the past 7 years, 50% of MERS-CoV cases reported to WHO were associated with human-to-human transmission in hospitals. Among 61 MERS-CoV patients presenting with MERS-CoV in 2017, 9 (15%) were associated with a hospital outbreak, 10 (16%) were household contacts, and 42 (69%) were sporadic cases. Of the 42 sporadic cases, 50% had camel contact.¹⁰⁵ In an outbreak investigation of a cluster of MERS cases in a nonhealth care–associated setting, 18 (2.2%) of 828 contacts were positive for MERS-CoV infections.¹⁰⁶ This rate was similar to household contact study of 4.3%.¹⁰¹

Intrahospital Transmission

Health care–associated infection is the hallmark of the transmission of MERS-CoV between patients and from patients to HCWs.^{69,70,74,81,107–123} Of the factors contributing to intrahospital transmission is the occurrence of superspreading events. In the outbreak in the Republic of Korea, three patients

were epidemiologically connected to 73% of the transmissions and each infected 23, 28, and 85 individuals.¹²⁴ In addition, superspreader phenomena also occurred in the first reported outbreak in Al-Hasa, Saudi Arabia.⁶⁹ A recent systematic review outlined the contributing factors to health care–associated MERS-CoV transmissions and included: absent physical barriers between beds, inadequate isolation of suspected MERS patients, lack of isolation and negative pressure rooms, unfamiliarity and underrecognition of MERS infection, insufficient compliance with infection control measures, aerosol generating procedures, presence of multiple friends and family members in the patient's room, and the phenomena of “medical shopping.”¹²⁵ HCWs may act as contributors to the spread of MERS-CoV infection. In one study, MERS-CoV PCR was positive in 4.5% among exposed HCWs¹²⁶ and another study showed 15 (1.3%) of 1,169 HCWs were positive by PCR and 5 (0.68%) of 737 HCWs were positive by serology.¹²⁷ Other studies showed none of 38 HCWs was positive by serology¹²⁸ and none of 48 contacts was positive.¹²⁹ In Korea, 36 (19.9%) of 181 confirmed MERS-CoV cases were HCWs.¹³⁰ However, studies had showed that most positive HCWs were asymptomatic or had mild disease.¹³¹ Although major hospital outbreaks were thought to be linked to intrahospital transmission of MERS-CoV, MERS-CoV genome sequence in these outbreaks showed multiple introductions of the virus with human-to-human transmissions.^{66,67,69} There were three distinct MERS-CoV genotypes.⁶⁷

Seasonality of MERS-CoV

The emergence of MERS-CoV had led to many speculations regarding the seasonality of this disease and initially thought to occur mostly in March–May and September–November.^{81,132,133} One reason for such a significant increase in April–May 2014 was a large outbreak in Jeddah, Saudi Arabia.¹⁰⁷ However, seasonal variation may be the result of seasonality in the calving of dromedaries in November and March.^{10,44,46,48,52,55,77,82,83,134} Such a concept was studied and it was found that the prevalence of MERS-CoV was higher in camels in the winter (71.5%) than the summer season (6.2%).¹³⁵ Looking at all MERS-CoV cases from 2012 to 2016, the mean monthly cases were

higher in the winter and summer months.¹³⁶ Evaluation of cases from January 2013 and December 2017 included a total of 2,025 cases and showed a noteworthy decrease in the annual cases in 2016 to 2017.¹³⁷ Of all the 2,025 cases, 38.2% occurred in the Spring and 36.4% occurred in the Summer.¹³⁷ However, there was no variation on the number of cases per year, and either per month or per season.¹³⁷

Therapeutic Options

Currently, there is no approved therapy for MERS-CoV infection. Studies showed superiority of interferon (IFN)- β compared with other IFN types¹³⁸ and that polyethylene glycol IFN- α had excellent cytopathic inhibitory effect.¹³⁹ In addition, the combination of IFN- α 2b and ribavirin showed augmentation of action and lower concentrations of IFN- α 2b and ribavirin were required.¹⁴⁰ However, the data from clinical use of these two agents in retrospective studies showed no therapeutic advantages of these on survival of patients.^{42,141–145} A retrospective analysis showed that using IFN to treat patients with positive MERS-CoV RT-PCR was associated with a case fatality rate of 90% compared with 44% in those with negative MERS-CoV RT-PCR test.⁶⁸ Another study showed survival rates of 78.3, 75, and 68.4% using IFN- β , IFN- α , and ribavirin, respectively.¹⁴⁶ The use of the antiretroviral therapy for MERS-CoV was tried using pegylated IFN, ribavirin, and lopinavir/ritonavir¹⁴³ and another eight patients received mycophenolate mofetil and the latter patients survived.¹⁴⁶ A randomized controlled trial using a combination of lopinavir-ritonavir and IFN- β 1b is being conducted.¹⁴⁷

Seroprevalence of MERS-CoV

Although MERS-CoV PCR testing is the main methodology for the diagnosis of MERS-CoV infection, serologic tests confirmed 8 (6.4%) of 124 Jordanian contacts who were positive.¹¹⁹ Seroprevalence of 356 abattoir workers and blood donors found that 8 (2.2%) were weakly positive by immunofluorescence assay (IFA), and none was had positive neutralization titers.¹⁴⁸ A seroprevalence study found none of 268 children with respiratory tract infections to be positive.¹⁴⁹ In an evaluation of 280 household contacts, 12 (4.3%) were probable cases by serology.¹⁰¹ However, in a population-based survey of 10,000 samples, the seroprevalence was 0.15% and the camel shepherd and abattoir workers had 17- and 26-fold increase in seroprevalence in comparison to the general population.¹⁵⁰

Infection Control

MERS-CoV is stable in the environment and can survive on plastic and steel for up to 48 hours at lower temperature and humidity. However, MERS-CoV is less viable at higher temperature and humidity.¹⁵¹ This finding was confirmed by another study where a temperature of 65°C had a strong negative effect on viral infectivity compared with a temperature of 25°C.¹⁵² In the hospital setting, WHO advocates

contact and droplet precautions with airborne isolation when dealing with aerosol-generating procedures.^{153,154} However, both the United States and the European Centre for Disease Prevention and Control recommend the use of airborne infection isolation precautions.¹⁵⁵

MERS and Camel Connections

In a recent study from Egypt, Senegal, Tunisia, Uganda, Jordan, Saudi Arabia, and Iraq, MERS-CoV was detected in camels using either PCR or serology.¹⁵⁶ The positivity rate using PCR ranged from 0% in Uganda, Jordan, and Iraq to 3.1% in Saudi Arabia, 5.5% in Senegal, and 8.2% in Egypt.¹⁵⁶ It was shown that seropositivity is very high (84.5%) among tested camels compared with PCR positivity of 3.8%.¹⁵⁷ Studies from Saudi Arabia showed either no significant difference in seropositivity of MERS-CoV in camels in different regions¹⁵⁶ or had detected variable seropositivity to MERS-CoV (37–100%).¹⁵⁸ It is worth mentioning that Somalia and Sudan are the main source of imported camels into Saudi Arabia.¹⁵⁶

The seroprevalence of MERS-CoV is lower (30.3%) in juvenile camels (<2 years of age) compared with adult camels (82.6%)¹⁵⁶ as described in the previous studies.⁵³ Also, the detection rate of MERS-CoV RNA by PCR is higher in adults (16.1%) compared with juvenile camels (1.7%).¹⁵⁶ What is unusual is the ability of MERS-CoV to cause reinfection of camels in the presence of antibodies.^{56,156} Another important finding of MERS-CoV in camels is that camels rarely show signs of infection.^{156,159} Although it has been postulated that drinking camel milk is one of the key sources of infection in the Arabian peninsula, a study found no MERS-CoV in the urine of naturally infected camels.¹⁶⁰

Conclusion

Emerging respiratory viruses, specially MERS-CoV, continue to challenge the public health infrastructure of countries of the Arabian Peninsula with the risk of transmission and outbreaks in other countries though travel. Although it is still debated by some, bats appear to be the common natural source of both SARS and MERS. There are considerable similarities in the clinical features of both MERS-CoV and SARS-CoV, but MERS tends to progress much faster to respiratory failure than SARS. Although SARS-CoV clinical cases disappeared since mid-2003, both MERS-CoV and SARS-CoV are still listed as priority pathogens by the WHO research and development blueprint. The case fatality rate of MERS-CoV is much higher and likely related to older age and comorbid illness of the sporadic cases. Several gaps continue in our knowledge about disease prevention and treatment, and more studies are needed to understand the pathogenesis, viral kinetics, mode of disease transmission, any other intermediary source, and treatment options of MERS to guide public health infection control measures and treatment.

Conflict of Interest

None declared.

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